

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bluestone JA, Anderson M. Tolerance in the age of immunotherapy. *N Engl J Med* 2020;383:1156-66. DOI: 10.1056/NEJMra1911109

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Supplemental Note 1. A second class of T cells, termed TCRgd cells, express a distinct T-cell receptor composed of a g and d heterodimer and the same associated CD3 complex chains. These cells, in general, do not see polymorphic MHC-peptide complexes but rather organic compounds produced by microbiota and, in some cases, mammalian cells. Importantly, these cells, as well as other innate-like T cells (MAIT [mucosal-associated invariant T cell] and NKT [natural killer-like T cell] cells) may be relevant to certain disease conditions (see below) but have not been as deeply studied in the context of tolerance induction and thus are not a focus of the review.

Supplemental Note 2. It should be noted that one of the most fundamental attributes of the immune tolerance system is its role in reproductive success in placental mammals. The maternal parent utilizes a number of the same tolerogenic pathways described above to circumvent immune-mediated rejection of the fetus leading to successful reproduction. In fact, it has been suggested that pregnancy imprints regulatory memory³³.